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# Deep neuromuscular blockade and low insufflation pressure during laparoscopic hysterectomy

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## ABSTRACT

**INTRODUCTION:** Establishment of sufficient muscle relaxation is essential in laparoscopic surgery. During laparoscopy, surgeons can experience abdominal contractions in their patients. Deep neuromuscular block (NMB) has the potential to prevent such episodes. In this study, we explored if deep NMB reduces the incidence of sudden abdominal contractions as compared with standard NMB.

**METHODS:** This was a pre-planned secondary analysis of a randomized, controlled study. A total of 110 patients scheduled for laparoscopic hysterectomy were randomized to either deep NMB and 8 mmHg pneumoperitoneum (deep NMB group) or single-bolus NMB and 12 mmHg pneumoperitoneum (standard NMB group). NMB was established with rocuronium and reversed with sugammadex. Two gynaecologists registered episodes of sudden abdominal contractions, alarms from the insufflator due to increased intra-abdominal pressure and incidences with tightness of the abdominal wall.

**RESULTS:** No sudden abdominal contractions were detected in the deep NMB group as compared with 12 episodes in the standard NMB group ( $p < 0.001$ ). The insufflator alarmed in no versus ten procedures ( $p = 0.001$ ) in the deep and standard NMB group, respectively. The gynaecologists registered increasing abdominal tensions in no versus eight procedures ( $p = 0.006$ ) in the deep and standard NMB group, respectively.

**CONCLUSION:** Deep NMB in combination with 8 mmHg pneumoperitoneum prevented sudden abdominal contractions during laparoscopic hysterectomy.

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**TRIAL REGISTRATION:** The study was assigned with EudraCT number 2012-003787-51 and registered with clinicaltrials.gov (NCT01722097).

ever, surgeons can experience incidents of patients having sudden abdominal contractions. These incidents carry a risk of damaging vital organs with the laparoscopic instruments because the contracting abdominal muscles drag the instruments inwards if the surgeon fails to remove them rapidly enough from the abdominal cavity. Administration of muscle relaxants to obtain a deep neuromuscular block (NMB), measured with a nerve stimulator, paralyzes all striated muscles including the diaphragm and the abdominal wall muscles. Therefore, deep NMB has the potential to prevent sudden abdominal contractions [3].

There are various methods of administering muscle relaxants, and use of muscle relaxants is not necessarily standard practice [4-6]. Some laparoscopic procedures are performed with administration of a single bolus of a muscle relaxant, which is followed by spontaneous neuromuscular recovery [7-9]. These procedures are chosen to minimize the risk of prolonged emergence from anaesthesia, awareness and post-operative residual muscle paralysis, which may cause respiratory complications [10, 11].

Recent studies indicate benefits of deep NMB on surgical conditions [6-8, 12]. In addition, combining a lower insufflation pressure with deep NMB during laparoscopic hysterectomy reduces the occurrence of shoulder pain [13]. However, performing laparoscopic surgery during low insufflation pressure [8] results in a narrower intraabdominal overview. In such cases it is therefore particularly pertinent to avoid sudden abdominal contractions since there is less space to move the instruments. In the present study, we report the influence of deep NMB in combination with a low insufflation pressure (8 mmHg) on the occurrence of sudden abdominal contractions compared with standard NMB (a single bolus of muscle relaxant) in combination with standard insufflation pressure (12 mmHg).

## METHODS

This was a pre-planned secondary analysis of a randomized, controlled, assessor-blinded study [13]. The study was approved by the Danish Medicines Agency and the local Research Ethics Committee. The study was as-

## ORIGINAL ARTICLE

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Laparoscopy is the preferred surgical technique in various types of abdominal surgery and has benefits compared with laparotomy including less pain and a shorter hospitalization period [1, 2]. During laparoscopy, how-

signed with EudraCT number 2012-003787-51 and registered with clinicaltrials.gov (NCT01722097). Written informed consent was obtained from all participants. Patients aged > 18 years scheduled for laparoscopic hysterectomy were eligible. The exclusion criteria were body mass index > 30 kg/m<sup>2</sup>, known allergy to medications that were included in the project, severe renal disease defined by glomerular filtration rate < 30 ml/min or S-creatinine concentration > 0.200 mmol/l, impaired liver function, neuromuscular disease interfering with the neuromuscular data, lactating women or indication for rapid sequence induction.

Patients were randomized to either deep NMB and 8 mmHg pneumoperitoneum (deep NMB group) or standard NMB and 12 mmHg pneumoperitoneum (standard NMB group) with stratification for type of hysterectomy (total or subtotal).

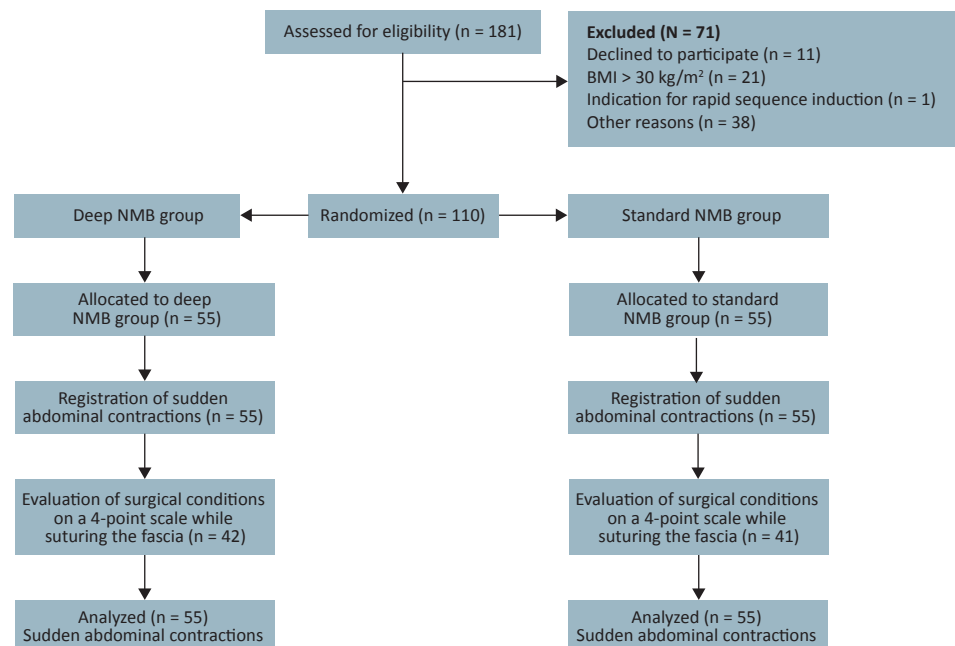
Our anaesthetic protocol has previously been reported [13]. In short, anaesthesia was induced and maintained with propofol and remifentanyl, adjusted under guidance of middle arterial blood pressure and a depth of anaesthesia monitor aiming at an entropy level of 30-50. Ventilation was performed with volume control mode with a tidal volume of 7 ml/kg, a frequency of 10-12/min and a positive end-expiratory pressure of 5 cm H<sub>2</sub>O aiming at normocapnia (end-tidal CO<sub>2</sub> 4.5-5.5 kPa). Neuromuscular monitoring followed good clinical research practice guidelines and depth of NMB was

monitored using train-of-four (TOF) and post-tetanic-count (PTC) ulnar nerve stimulation [14]. Tracheal intubation was performed 2 min after administration of the muscle relaxant 0.3 mg/kg rocuronium. In patients allocated to deep NMB, a bolus of 0.7 mg/kg rocuronium was administered immediately after intubation, and infusion of rocuronium (0.3-0.4 mg/kg/h) was started when PTC > 0 and titrated toward PTC 0-1. In patients allocated to standard NMB, a similar volume of saline 0.9% was given and infusion of saline 0.9% (2-3 ml/kg/h) was started after 20-30 min. In the standard NMB group, no supplemental rocuronium was administered, unless requested by the gynaecologist.

The investigator managed the insufflation of the abdomen to either 8 or 12 mmHg pneumoperitoneum. The insufflator alarm was activated if the pressure exceeded 5 mmHg of the pre-set pressure. Patients were placed in the lithotomy position in a 30-degree head-down body position. The same two gynaecologists working together performed all operations and were instructed in registering any sudden patient movement, any alarms from the insufflator indicating increased intra-abdominal pressure and any incidences in which the abdominal wall felt tight. In cases in which the surgical overview was considered unacceptable, the protocol allowed the pneumoperitoneum to be increased to 12 mmHg in combination with a bolus of saline in patients allocated to the deep NMB group. In the standard NMB group, the

 **FIGURE 1**

Flow chart of the study.  
NMB = neuromuscular block.



protocol allowed the investigator to pretend that the pneumoperitoneum was increased by managing the insufflator (placebo increasing pneumoperitoneum) in combination with 0.6 mg/kg bolus of rocuronium. If none of these interventions improved the surgical overview, the gynaecologists could decide on an intervention according to their usual clinical practice. Immediately after closure of the abdominal wall fascia, the gynaecologists evaluated the surgical conditions on a four-point rating scale (1: excellent, 2: good, 3: acceptable, 4: poor) [8].

After insertion of the last suture, NMB was antagonized with sugammadex, if needed. Blinding of the gynaecologists regarding level of NMB and the level of pneumoperitoneum was ensured by turning the insufflator and covering the display. Also, the hand with the neuromuscular device was covered. The attending anaesthetist, the investigator and the operating nurses were not blinded.

The primary outcome was the incidence of sudden abdominal contractions. Other outcomes were incidences of insufflator alarms due to increased intra-abdominal pressure, incidences of increasing abdominal wall tension and surgical conditions during abdominal fascia closure using a four-point rating scale.

The patients' case files were reviewed on the 21th post-operative day to identify any adverse events or reactions. Adverse events or reactions were considered serious if fatal and life-threatening if they had caused permanent disability or required prolonged hospitalization.

The study was conducted according to the International Conference on Harmonization/Good Clinical Research Practice guidelines [15].

### Statistical analysis

Normally distributed data were described with mean and standard deviation. Non-normally distributed data were described with median and range. Fisher's exact test was used for comparing groups with respect to the primary outcome. The association between the rating of surgical conditions and allocation to level of NMB was tested with the Mann-Whitney U test.  $p < 0.05$  was considered statistically significant.

The gynaecologists estimated that they experienced abdominal contractions in every second patient in the standard NMB group during laparoscopic hysterectomy. It was estimated that the incidence of sudden abdominal contractions could be reduced from 50% to 10% with a deep NMB and 8 mmHg compared with a standard NMB and 12 mmHg. With a power of 0.90 and a 5% risk of type 1 error, 26 patients needed to be included in each group to detect a 40% difference. However, outcomes were collected from 110 patients as they also

TABLE 1

Patient characteristics.

	Deep NMB group (N = 55)	Standard NMB group (N = 55)
BMI, kg/m <sup>2</sup> , mean ( $\pm$ SD)	23.1 ( $\pm$ 3.0)	24.2 ( $\pm$ 3.1)
Age, yrs, mean ( $\pm$ SD)	47 ( $\pm$ 5.0)	48 ( $\pm$ 5.0)
Parity, full-term pregnancies, n, median (range)	2 (0-4)	2 (0-4)
Previous intra-abdominal surgery, n (%)	26 (47.3)	35 (63.6)
Hysterectomy, n (%)		
Total	29 (52.7)	28 (51)
Subtotal	26 (47.3)	27 (49)

NMB = neuromuscular block; SD = standard deviation.

TABLE 2

Events during laparoscopy in the deep and standard neuromuscular block groups.

	Deep, n (%) (N = 55)	Standard, n (%) (N = 55)	ARR (95% CI)	p-value <sup>a</sup>
Sudden abdominal contraction	0	12 (21.8)	0.22 (0.11-0.34)	< 0.001
Insufflator alarm	0	10 (18.2)	0.18 (0.07-0.30)	0.001
Increased abdominal wall tension	0	8 (14.5)	0.14 (0.05-0.26)	0.006

ARR = absolute risk reduction; CI = confidence interval.

a) Fisher's exact test.

participated in the trial "Post-operative shoulder pain after laparoscopic hysterectomy with deep neuromuscular blockade and low intraabdominal pressure – a randomized controlled trial (NCT01722097)" [13]. Accordingly, 110 patients were recruited.

**Trial registration:** The study was assigned EudraCT number 2012-003787-51 and registered with clinicaltrials.gov (NCT01722097).

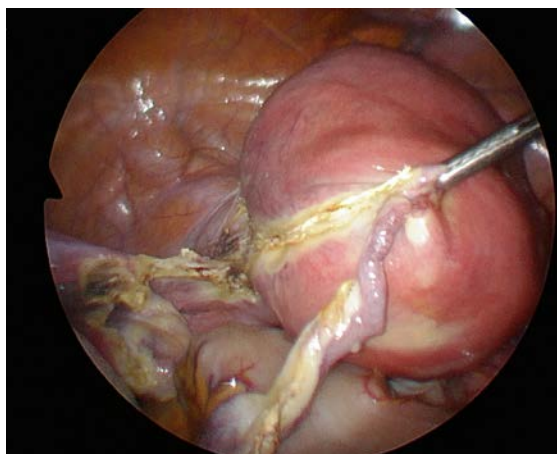
### RESULTS

During the study period, a total of 181 patients were eligible of whom 71 were excluded (**Figure 1**). Patient characteristics are reported in **Table 1**.

No sudden abdominal contractions were detected in the deep NMB group as compared with 12 episodes in the standard NMB group ( $p < 0.001$ ). The insufflator alarmed in no versus ten procedures ( $p = 0.001$ ) in the deep and the standard NMB group, respectively. The gynaecologists registered increasing abdominal tensions in no versus eight procedures ( $p = 0.006$ ) in the deep and the standard NMB group, respectively. A total of 19 (35%) patients in the standard NMB group had episodes of sudden abdominal contractions, insufflator alarms or increasing abdominal wall tensions (**Table 2**).

When events occurred, corresponding TOF ratios were within the range of 58-129% (median 103%), and

Laparoscopic  
hysterectomy.



the entropy values were within the range of 22-98 (median 37). When events occurred, 11 of 19 patients had entropy values between 30-50 as set by our protocol. No patients had intraoperative awareness.

In the standard NMB group, 46 (84%) patients had recovery of NMB [14] upon application of pneumoperitoneum (insertion of Veress needle). Five (9%) patients had a moderate NMB (TOF count 1-3 [14]). In four (7%) patients, NMB never reached a moderate level after administration of 0.3 mg/kg rocuronium. The average operating time (from insertion of Veress needle to last suture) in the standard NMB group was 70 (range: 42-148) min. On average, 87% (range: 59-100%) of the operating time was performed without NMB (TOF ratio > 0.9) in the standard NMB group. A total of 41 of 55 patients (75%) in the standard NMB group had at least 80% of surgery performed with no NMB.

In 83 patients, the abdominal fascia was sutured and surgical conditions were evaluated. Deep NMB significantly improved surgical conditions estimated on a four-point rating scale while suturing the abdominal fascia ( $p < 0.001$ ) (Table 3). There was no difference in the duration of surgery (65 min in the deep NMB group versus 70 min in the standard NMB group ( $p = 0.624$ ), respectively [13]. All operations were completed according to allocation, i.e. there was no need to either increase intraabdominal pressure or administer a bolus of muscle relaxant.

We registered adverse events requiring hospitalization in seven patients: Three with infection (two in the deep NMB group), one with lesion of the bladder (deep NMB group), which was sutured and repaired during surgery, one with a vesico-vaginal fistula (standard NMB group) which developed three weeks after the primary surgery and one with post-operative bleeding (standard NMB group) requiring repeated surgery. One patient (deep NMB group) with two previous Caesarean sections and heavy adhesions had both a haematoma and infec-

TABLE 3

Surgical conditions while suturing the fascia. The values are number of patients.

Ratings***	Deep NMB group	Standard NMB group
1: excellent	40	23
2: good	2	17
3: acceptable	0	1
4: poor	0	0

NMB = neuromuscular block.

\*\*\*) Mann-Whitney U:  $p < 0.001$ .

tion post-operatively and developed a vesico-vaginal fistula six weeks after the primary surgery.

## DISCUSSION

We found that deep NMB and pneumoperitoneum 8 mmHg compared with standard NMB and pneumoperitoneum 12 mmHg prevented sudden abdominal contractions during laparoscopic hysterectomy. Moreover, deep NMB and pneumoperitoneum 8 mmHg improved surgical conditions during suturing of the abdominal fascia compared with standard NMB and pneumoperitoneum 12 mmHg.

Our findings are important, especially for laparoscopic hysterectomy since the establishment of a steady operating field is crucial, e.g. during morcellation where a rotating knife is used inside the abdomen. However, establishment of deep NMB throughout the procedure was unable to prevent adverse events such as bladder lesion, development of haematoma and vesico-vaginal fistula. In addition, these cases were regarded as extremely complicated due to previous Caesarean sections with heavy adhesions as well as deeply located retroperitoneal fibroids. According to the surgeons, these cases developed independently of the level of NMB.

A systematic review found that deeper levels of NMB compared with more moderate levels of NMB improve subjective ratings of surgical conditions during certain laparoscopic procedures [16]. Our results are in accordance with these findings, though the majority of patients in the standard NMB group received only a shallow level of block and most of them were unparalysed during major parts of the surgery since the surgeons did not request additional boluses of muscle relaxant.

One of the strengths of this study was the blinding of the gynaecologists who registered the incidences of sudden abdominal contractions and assessed the surgical conditions. However, the lack of incidences in the patients receiving continuous deep NMB may also have introduced bias in the subjective ratings after suturing of the fascia. Another important limitation of the study was

that two interventions were applied (level of pneumoperitoneum and level of NMB). We are therefore able only to reach conclusions about the combination of level of NMB and the level of pneumoperitoneum. The reason why we used two interventions was that this study was also designed to investigate other parameters that have been reported separately [13].

We compared deep NMB (PTC 0-1) with a standard NMB regimen defined as spontaneous recovery after a single dose of rocuronium as this is usual care at the institution where the study was conducted. When patients have sudden movements during surgery, the first anaesthetic choice is often to administer a bolus of opioid or to increase the depth of anaesthesia. This may, however, have a negative cardiovascular effect and may also not always successfully prevent sudden movements [17]. In contrast, a relevant concern about NMB is the risk of awareness [10, 18], residual paralysis and prolonged emergence from anaesthesia [19]. Therefore, regardless of depth of NMB, use of NMB is recommended only in properly anaesthetized patients along with objective neuromuscular monitoring and correct reversal of the NMB [20].

## CONCLUSIONS

Deep NMB in combination with 8 mmHg pneumoperitoneum prevented sudden abdominal contractions during laparoscopic hysterectomy. Moreover, deep NMB in combination with 8 mmHg pneumoperitoneum improved surgical conditions while suturing the abdominal fascia.

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